Remarks

Claims 1-18 are pending. Claim 2 has been canceled. Claims 1, 4-6, and 8-10 have been amended. New claims 19-28 have been added. Support for the new claims and claim amendments can be found throughout the specification. No new matter has been added.

Amendment of claims should in no way be construed as an acquiescence to any of the Examiner's rejections. The amendments to the claims are being made solely to expedite prosecution of the present application. Applicants reserve the option to further prosecute the same or similar claims in the instant or in a subsequent patent application.

Rejection of claims 1-14 under 35 U.S.C. 112, first paragraph, written description

Claims 1-14 were rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way to reasonably convey to one skilled in the relevant art that the inventor(s) at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection.

Applicant respectfully submits that there is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed (Revised Interim Written Description Guidelines Training Materials). Applicant further submits that a person of skill in the art would recognize from the disclosure that Applicant was in possession of the claimed invention at the time the application was filed.

Claim 1 is drawn to a method for preventing or treating a disease or condition caused, or contributed to, by lipolysis or elevated FFA levels in a subject, comprising administering to the subject a pharmaceutically effective amount of an inhibitor of a MAPK pathway to reduce lipolysis, to thereby prevent or treat the disease or condition in the subject.

A representative number of ERK1/2 inhibitors are explicitly disclosed in the specification. The specification describes numerous species of MAPK pathway inhibitors. In particular, the specification describes that an inhibitor of a kinase can be:

> any molecule which decreases the activity of the kinase or decreases the protein level of the kinase. Thus, a kinase inhibitor can be a small molecule which decreases activity of the kinase, e.g., by interfering with interaction of the kinase with another molecule, e.g., its substrate. It can also be a small molecule which decreases expression of the gene encoding the kinase. An inhibitor can also be an antisense nucleic acid, a ribozyme, an antibody, a dominant negative mutant of the kinase, or a phosphatase.
>
> Page 9, lines 18-23.

The specification elaborates on all of these inhibitors. In addition, as acknowledged by the Examiner, the specification discloses that several species of MAPK pathway inhibitors were reduced to practice. For example, the specification discloses that PD98059 and NaSal inhibit the MAPK pathway and inhibit lipolysis. Sufficient inhibitors are described that a person of skill in the art would recognize that Applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed or claimed. Applicant notes that the particular structure of the different inhibitors is not a necessary common attribute of the elements possessed by the members of the genus.

The Examiner states that "[t]here is a high level of unpredictability in the art for design of specific MAPK gene and protein inhibitors." Applicant respectfully submits that antisense, ribozyme and other gene inhibitors can be designed and tested according to methods known in the art. Designing such molecules is considered conventional in the art, it is a routine-art-recognized technique. The level of skill in the art is high. Even if, e.g., certain antisense molecules are not functioning adequately, a person of skill in the art can find others that will without undue experimentation.

Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Rejection of claims 1-14 under 35 U.S.C. 112, first paragraph, enablement

Claims 1-14 were rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully traverse this rejection.

The Examiner states that "there is a high level of unpredictability that the inhibitors taught in the specification as filed would function in a whole organism as claimed." The Examiner adds that "[o]ne of the inhibitors taught in the specification a filed, PD098059, was shown to have no effect on noradrenaline-stimulated lipolysis as taught by Fryer et al." It is respectfully submitted that the specification demonstrates that PD098059 inhibits TNF-α-induced lipolysis. In addition, Applicant demonstrated that ERK1/2 inhibitors also inhibit basal lipolysis (see, e.g., specification at page 62, lines 3-6 and Applicant's publication Zhang et al. (2001) Scientific Sessions, Diabetes, A13:49-OR, attached hereto as Exhibit I). Applicant has also demonstrated that PD098059 blocks catecholamine-, forskolin-, and CL316,243-, a beta-3 agonist, stimulated lipolysis by 50% (see Applicant's publication Shen et al. (2001) Scientific Sessions, Diabetes, A13:51-O, attached hereto as Exhibit II). Regarding Fryer et al., this reference does not show that noradrenaline-stimulated lipolysis is not inhibited by PD098059.

The paragraph discussing the effect of PD098059 is at page 516, second paragraph under "Signaling mechanisms for insulin's action on lipolysis." In this paragraph, the authors state that they examined whether there was any involvement of the MAP kinase pathway in the anti-lipolytic effect of insulin. The authors conclude that "PD098059 had no effect to impair insulin's inhibition of lipolysis..." (emphasis added). The fact that the authors describe the effect of PD098059 on insulin's inhibition of lipolysis is also evidenced by Fig. 4 at page 518, that shows that PD098059 was added to cells treated with noradrenaline and insulin and to cells treated with noradrenaline only. Thus, since insulin inhibits noradrenalin-stimulated lipolysis, the effect of PD098059 on cells treated with noradrenaline and insulin would be hidden by the effect of insulin. Thus, Fryer et al. do not teach that PD098059 does not inhibit noradrenalin-stimulated lipolysis. Thus, contrary to the Examiner's statement, there is no variability in the ability of known MAPK inhibitors to function to decrease lipolysis.

The Examiner states that "such known inhibitors are generally not specific for any one component of the MAPK pathway and are known to have many possible physiological changes in a whole organism." The Examiner failed to provide any evidence supporting this statement. Applicants respectfully submit that MAPK pathway inhibitors are specific for particular components of the MAPK pathway. For example, PD098059 is known to inhibit MEK1, which is an activator of ERK1/2 (see, e.g., page 60, lines 4-5, of the specification). In addition, this inhibitor is highly selective, and does not appreciably inhibit the following kinases at 50 μM concentration: MAP kinase; protein kinase C, v-Src; EGFR tyrosine kinase; NGFR (trk-A) tyrosine kinase; PDGFRβ tyrosine kinase; PI-3 kinase; *E. coli* histidine kinase NRII; and Raf (see, col. 9, lines 31-40 of US. Patent 5,525,625, attached hereto as Exhibit III; wherein PD098059 is referred to as 2'-amino-3'-methoxyflavone). It also shows selectivity between biological activities, e.g., between the mitogenic and metabolic effects of insulin (see, col. 8, lines 60-61 of U.S. patent 5,525,625). Similarly, another MEK inhibitor, U0126, described in Favata et al. (1998) J. Biol. Chem. 273:18623 (attached hereto as Exhibit IV), shows a high selectivity towards MEK1 and MEK2. It does not significantly inhibit any of the following kinases: protein kinase C., Abl, Raf, MEKK, ERK, JNK, MKK3, MKK6, Cdk2 and Cdk4 (Favata et al., *supra*). Thus, contrary to the Examiner's assertion, inhibitors of the MAPK pathway can be specific for any one component of the MAPK pathway.

Regarding the Examiner's statement that MAPK inhibitors "are known to have many possible physiological changes in a whole organism," no supporting evidence was provided either. Contrary to this statement, Applicants submit that at least one member of the MAPK pathway is the target of a drug that is in Phase II clinical trials. The inhibitor is an antisense molecule targeted to Raf (which activates MEK) that is produced by ISIS Pharmaceuticals, Inc.

(ISIS 5132). Even if some inhibitors may have undesirable physiological changes in a whole organism, the specification teaches how to conduct *in vitro* and *in vivo* tests to determine undesirable physiological changes. For example, *in vitro* assays for determining the effect of a compound on lipolysis are described, e.g., in the Examples and at pages 38 and 39 of the specification. These assays would reveal whether an inhibitor has undesirable properties. In addition, the specification teaches, e.g., at page 49, lines 13-22, various animal models, well known in the art, which can be used to test MAPK pathway inhibitors without undue experimentation. Such animal models would reveal the existence of undesirable physiological changes in a whole organism. Clinical trials would also reveal undesirable properties that certain inhibitors may have. Applicant notes that there is no requirement that clinical trials be conducted for patentability. In addition, the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. M.P.E.P. 2164.08(b). As indicated above, a person of skill could determine which embodiments would be inoperative or operative with expenditure of no more effort that is normally required in the art. Thus, the claims are enabled.

The Examiner further states that "[t]he other inhibitors taught in the specification were pre-administered to the cells in culture prior to stimulation of lipolysis by TNF-alpha" and that "[f]or these examples, there is no established correlation between administration of any possible inhibitor to cells in cell culture and administration to whole organisms as broadly claimed." It is respectfully submitted, that Applicant has demonstrated that pretreatment of cells with MAPK inhibitors results in inhibition of lipolysis. Thus, treatment of a whole organism with MAPK inhibitors would at least prevent the appearance of lipolysis in cells that have been contacted with the MAPK inhibitor prior to being contacted with the agent inducing lipolysis. Thus, contrary to the Examiner's statement, a person of skill in the art would expect a treatment effect from looking at the effects of pre-treated cell culture cells. Furthermore, as indicated in the attached Declaration under 37 C.F.R. 1.132 by Andy S. Greenberg, MAPK pathway inhibitors also inhibit lipolysis in the absence of pretreatement.

The Examiner also states that "neither the specification nor the art teach inhibition of a specific component of a MAP pathway having correlation to a direct reduction of a specific lipolysis condition in a whole organism, one skilled in the art would not have been able to practice the methods of treatment broadly claimed for treatment of any lipolysis in any whole organism with any inhibitor of any MAPK pathway component." Applicants respectfully submit that there is a reasonable correlation between the claimed therapeutic methods and the in vitro examples provided in the specification, that is, the claimed methods would be convincing to a person of skill in the art based on the *in vitro* results. A person of skill in the art would be

without basis to reasonably doubt Applicant's asserted utility on its face. The Examiner has not provided any evidence to the contrary, and has not satisfied its initial burden. Applicant has demonstrated that several inhibitors of MAPK pathways reduce lipolysis of cells *in vitro.* Applicant has also demonstrated that the activity of ERK1/2 is inhibited in adipocytes by the MAPK pathway inhibitor used (see, e.g., Figs. 3, 6A and 7A-C). Accordingly, the claimed methods would be credible to a person of skill in the art.

To further substantiate any doubt as to the asserted utility, the Applicant has shown that inhibition of the MAPK pathway in fresh human adipocytes results in inhibition of basal and TNF-α induced lipolysis (see attached Declaration Under 37 C.F.R. 1.132 by Andrew S. Greenberg). As further described in the Declaration, the Applicant has also demonstrated that another inhibitor, U0126 (Favata et al., supra), which is a stronger inhibitor than PD098059, inhibits basal and TNF-α induced lipolysis in fresh human adipocytes to a higher extent than PD098059. Also, the Applicant has demonstrated inhibition of lipolysis with a recombinant adenoviral vector encoding a dominant negative Erk-1 (see attached Declaration). The Declaration does not render an insufficient disclosure enabling, but instead goes to prove that the disclosure was in fact enabling when filed (In Re Brana, 51 F.3d 1560, 1567, 34 U.S.P.Q. 2d 1436 (1995, Fed. Cir.)).

Applicant also notes that in vitro assays using cells affected by a particular disease, e.g., cell lines or fresh tissue from a patient, are standard in the art of identifying therapeutics for that particular disease. In the instant case, adipocytes are known to be the cells that are subject to lipolysis in humans, which cells, upon lipolysis release free fatty acids (FFAs) and glycerol, thereby causing diseases, e.g., insulin resistance. Thus, based on the Examples in the application, which describe that inhibitors of the MAPK pathway block lipolysis in adipocytes, a person of skill in the art would not doubt the asserted utility of treating a subject with such inhibitors for treating diseases resulting from lipolysis of adipocytes.

The Examiner also states that "[i]n regards to design of antisense, ribozyme or other gene inhibitors for instance, there is a further high level of unpredictability for design of such inhibitors which target a gene and function in a whole organism for treatment purposes as instantly claimed." It is respectfully submitted that antisense, ribozyme or other gene inhibitors are drugs like any other conventional drugs. Even if they may not be considered "magic bullets" by some, "there is growing evidence that antisense molecules can be useful as pharmacological tools when applied carefully" (see page 50 of A. Branch, citing Crooke et al. (1996) Annu. Rev. Pharmacol. Toxicol. 36:107). Branch also describes a Phase III clinical trial of patients with cytomegalovirus-associated retinitis with antisense molecules (Branch, page 46, middle of left column). Even if some antisense molecules may have non-antisense effects, these effects may

actually be beneficial for treatments (see, e.g., Branch, page 46, left of first column). Regarding the quote from Flanagan et al., cited by the Examiner, Flanagan et al. state that antisense oligonucleotides do not seem to reach solid tumors when administered intravenously (see page 51, right column; emphasis added). However, solid tumors are not the target site in the claimed method. Furthermore, Flanagan et al. state that,

> [i]n contrast to tissue culture studies, numerous animal studies have reported that conventional oligonucleotides (20-28 nucleotides long phosphorothioate oligonucleotides) can penetrate cells and demonstrate antisense effects in a variety of cell types without the aid of delivery agents (Monia et al. (1996) Nat. Med. 2:668; McKay et al. (1994) PNAS91:1762; Stepkowski et al. (1994) J. Immunol. 5336 and Plenat (1996) Mol. Med. Today 2:250). These animal results have helped to validate the technology for use as human therapeutics and have resulted in several oliogonucleotides entering clinical trials (W. Flanagan (1998) Cancer and Metastasis Rev. 17:169).

Thus, even if certain oligonucleotides may not be distributed and internalized equally among organs and tissues, the cited references provide no evidence that antisense molecules would not reach and enter target cells in the claimed treatment. On the contrary, the references indicate that antisense molecules can be used in whole organisms.

In addition, numerous antisense and ribozyme products are currently in clinical trials or have been approved. For example, ISIS Pharmaceuticals has an antisense for AIDS-related CMV retinitis (Vitravene) that is approved in the U.S. for clinical use. The company also has conducted Phase II clinical trials with antisense molecules to the following genes: PKC-alpha; c-raf kinase and Ha-ras kinase, all for treating cancer (see, e.g., www.biospace.com/articles/isis.cfm). Several other antisense drugs are in Phase I or preclinical testing. Other companies, e.g., Enzo Biochem. Inc. and Genta Inc. are also testing antisense molecules in clinical trials (see, e.g., www.biospace.com/articles/072899.table1.cfm). Ribozymes are also currently in clinical trials. For example, Ribozyme Pharmaceuticals, Inc. has the following ribozymes in clinical trials: ANGIOZYME®, an inhibitor of angiogenesis, HEPTAZYME™, an anti-hepatitis C anti-viral compound and HERZYME™ for the treatment of breast cancer (see, e.g., www.rpi.com/portfolio.cfm).

Thus, one skilled in the art would be able to make and use the claimed invention using the application as a guide. Applicant notes that the evidence provided by Applicant need not be conclusive, but merely convincing to one skilled in the art. M.P.E.P. 2164.05. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Rejection of claims 15-18 under 35 U.S.C. 103(a)

Claims 15-18 were rejected under 35 U.S.C. 103(a) as being unpatentable over Souza et al. (IDS Ref. AX), Klein et al. (U.S. Patent No. 6,255,059), Momose et al. (U.S. Patent No. 6,110,948), Marshall et al. (IDS Ref. AM) and Davis et al. (IDS Ref. AP). Applicants respectfully traverse this rejection.

Claims 15-17 are drawn to a method for determining whether a subject has or is likely to develop a disease or condition cause, or contributed to by lipolysis, comprising determining the activity of an ERK 1/2 and/or JNK in the individual. Claim 18 is drawn to a drug screening method for identifying a compound which reduces TNF-α induced lipolysis comprising (i) isolating a compound which is an ERK 1/2 and/or JNK inhibitor; (ii) contacting an adipocyte with the compound of step (i) and TNF-α and determining the level of lipolysis.

Souza et al. is relied upon by the Examiner as teaching "methods of testing the effects of TNF-alpha and BRL 49653, an agonist of PPAR-gamma2 receptor, on adipocyte lypolysis (see abstract)." The Examiner acknowledged that "[t]hey do not specifically teach looking for changes in ERK 1/2 and/or JNK expression for inhibition of lipolysis."

Klein et al. is relied upon as teaching "methods for screening G-protein coupled receptors for agonists and antagonists." The Examiner acknowledges that "[t]hey do not necessarily teach analysis of protein levels from a subject as a diagnosis."

Momose et al. is relied upon by the Examiner as teaching "suppression of lipolysis in mice treated with diuretics such as sodium salicylate." The Examiner acknowledges that "[t]hey do not specifically teach analysis of protein levels from a subject as a diagnosis."

Marshall et al. and Davis et al. are relied upon by the Examiner as teaching "methods of screening for compounds which modulate MAPK pathway components having potential therapeutic benefits." The Examiner acknowledges that "[t]hey do not necessarily teach the involvement of MAPKs in lipolysis."

It is the Examiner's position that "[i]t would have been prima facie obvious at the time the invention was made for one of ordinary skill in the art to determine the activity of an ERK 1 or 2 and/or JNK in an individual for connection to lipolysis and screen for inhibitors of ERK 1/2 or JNK to identify a compound which reduces lipolysis since the role of MAPK kinases such as ERK 1/2 or JNK in connection to lipolysis was known in the art as taught by Souza et al., and methods of screening members of MAPK pathways were well known in the art as taught by Klein et al., Momose et al., Marshall et al. and Davis et al. Klein et al. and Momose et al. further taught screening for agents involved in lipolysis."

Applicant respectively submits that the Examiner acknowledged that Souza et al. "do not specifically teach looking for changes in ERK 1/2 and/or JNK expression for inhibition of lipolysis." As further indicated in the Souza et al. reference, this reference does not, contrary to the Examiner's allegation, teach "the role of MAPK kinases such as ERK 1/2 or JNK in connection to lipolysis." Accordingly, the Examiner failed to establish a *prima facie* case of obviousness, since the Examiner failed to provide any evidence of sufficient motivation to combine the cited references. Furthermore, contrary to the Examiner's statement, there would not have been any reasonable expectation of success to establish claimed diagnostic assays and drug screening methods, because the involvement of MAPK kinases, such as ERK 1/2 or JNK in lipolysis was not known prior to the Applicant's discovery thereof.

Thus, reconsideration and withdrawal of this rejection is respectfully requested.

Conclusion

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-832-1000.

Respectfully submitted,
FOLEY, HOAG, & ELIOT

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Copy of amended claims with changes marked thereon:

1. **(Amended)** A method for preventing or treating a disease or condition caused, or contributed to, by lipolysis or elevated FFA levels in a subject, comprising administering to the subject a pharmaceutically effective amount of an inhibitor of a [MAPK pathway] ERK1/2, a MEK or a JNK to reduce lipolysis, to thereby prevent or treat the disease or condition in the subject.

4. **(Amended)** The method of claim 3, wherein the inhibitor decreases the protein level of ERK1/2, a MEK and/or a JNK.

5. **(Amended)** The method of claim 4, wherein the inhibitor decreases expression of a gene encoding ERK1/2, a MEK and/or a JNK.

6. **(Amended)** The method of claim 5, wherein the inhibitor interacts with an ERK1/2, a MEK and/or JNK gene.

8. **(Amended)** The method of claim 3, wherein the inhibitor decreases the activity of ERK1/2, a MEK and/or a JNK.

9. **(Amended)** The method of claim 6, wherein the inhibitor interacts with ERK1/2, a MEK and/or a JNK protein.

10. **(Amended)** The method of claim 6, wherein the inhibitor inhibits ERK1/2, a MEK and/or JNK phosphorylation.